

REMARKS

Reconsideration of the allowability of the present application in view of the above claim amendments and the following remarks is requested respectfully.

Discussion of the Claims

In his Action, the Examiner acted upon Claims 1 to 8, 16, 20 to 22, 26, and 29 of the application, Claims 9 to 15, 17 to 19, 23 to 25, 27, 28, and 30 to 52 having been withdrawn previously from further consideration as being directed to non-elected species. This withdrawal is subject to being rescinded should claims generic to the non-elected species be found allowable. MPEP §809.02(c).

Claims 1, 29, and 30 have been amended. Claim 2 has been cancelled. No claims have been added.

The claims pending presently are Claims 1 and 3 to 52.

Discussion of the Amendments

Claims 1 and 30 have been amended to define the single-chain polypeptide as being an sFv polypeptide. Support for this amendment is found in the application in the paragraph that bridges pages 13 and 14 and in the Examples section.

Claim 29 has been amended to define the compound as being one which targets a cell which expresses erbB-2. Support for this amendment is found in the application at Example 8.

No new matter has been added.

Applicants advise that no claim has been added with the present amendment and that one claim was cancelled and three claims were amended to place them in a better form for consideration on appeal. As the amendment to Claims 1 and 30 incorporates therein a recitation previously found in now cancelled Claim 2 and as the amendment to Claim 29 recites a property which is inherent to the compound defined therein and which is discussed in the descriptive portion of the application, no new search is required. Accordingly, applicants request respectfully the entry of the above amendments.

Discussion of the Examiner's Section 102(b) Rejection

In the Action, the Examiner advised that he has withdrawn his previous rejection of independent Claim 1 and related dependent Claims 3 and 4 as being anticipated by Wagner et al., *PNAS USA*, 87: 3410-3414 (1990). However, he advised also that the withdrawal was based on the claim as amended in the October 5, 2005 Reply and that the amendment had added "new matter".

Applicant disputes that the amendment added "new matter". Regardless of that, however, Claim 1 has presently been amended again to define the compound therein as being one which comprises a polypeptide which comprises an sFv molecule and at least one effector segment which includes at least one cysteinyl residue and a nucleic acid-binding moiety coupled to the polypeptide by the cysteinyl residue. As Wagner et al. does not disclose such a compound but rather discloses a compound comprising transferrin and a nucleic acid-binding moiety, it does not anticipate Claim 1 as

amended.

Traversal of the Examiner's Section 103 Rejection

The Examiner rejected Claims 1, 3 to 8, 16, 20 to 22, 26, and 29 as being unpatentable over the disclosure of the aforementioned Wagner et al. publication in view of U.S. Patent No. 5,977,322 to Marks et al., and International Application Publication No. WO 00/04922 to Konadu et al.

To establish a *prima facie* case of obviousness, the Examiner must show that one skilled in the art would have, given the disclosures of the cited references, had a reasonable expectancy that the invention would work for its intended purpose. MPEP § 2143. Applicants submit respectfully that this has not been shown.

Independent Claim 1, from which Claims 3 to 8, 16, 20 to 22, 26, and 29 depend, recites a gene-delivery compound comprising a polypeptide which comprises an sFv molecule and at least one effector segment which includes at least one cysteinyl residue and a nucleic acid-binding moiety which is coupled to the polypeptide by the cysteinyl residue. Wagner et al. discloses a compound comprising transferrin coupled with salmon protamine wherein the coupling is achieved using SPDP as a heterobifunctional cross-linking agent. Marks et al. discloses a chimeric molecule comprising an effector molecule and an sFv. Konadu et al. describes the use of SMCC as a heterobifunctional cross-linking agent to bind an oligosaccharide to a carrier. According to the Examiner, one skilled in the art would have been motivated by the teaching of Marks et al. to modify the compound of Wagner et al. by substituting sFv for the transferrin therein and by Konadu et al. to use SMCC as the heterobifunctional cross-linking agent. According also to the Examiner, one skilled in the art would have

had a reasonable expectation of success as cross-linking sFv to salmon protamine is a routine technique and is only a “minor modification” to the compound taught by Wagner et al.

Applicants disagree respectfully with the Examiner and believe that the present rejection is based on a hindsight reconstruction of the present invention based on picking and changing components in the cited art to construct applicant’s compound. In particular, there is nothing in the combined disclosures of the cited art to lead one skilled in the art to believe that a polypeptide comprising an sFv molecule may be coupled with a nucleic acid binding moiety nor is there motivation to combine these components together. Even if the Examiner assumes that one skilled in the art would have been motivated to use a polypeptide comprising the sFv molecule and an effector segment comprising a cysteinyl residue (and he does not discuss the use of such an effector segment) and couple that with the nucleic acid binding moiety, there is no reasonable expectation that such a compound would work for its intended purpose. In the first instance, there is no expectation that such a compound would be stable. The stability of such a conjugated compound depends on many factors, for example, whether steric hinderance caused by one moiety against the other might prevent the two moieties from conjugating and whether the conjugated moieties may remain conjugated when introduced into *in vivo* conditions. Further, even if the two moieties are conjugated, it is unpredictable whether the final compound would successfully serve to bind a nucleic acid or an antigen since the conformation of the combined molecule might prevent a nucleic acid from binding to it or prevent the molecule from binding to an antigen. As none of the cited art discloses a molecule in which both a nucleic acid binding moiety and a polypeptide comprising an sFv are conjugated, one skilled in the art would not have had any expectancy as to the success of the present invention.

**Discussion of the Examiner's Rejection  
Under the Written Description Requirement of Section 112, First Paragraph**

The Examiner rejected Claims 1, 3 to 8, 16, 20 to 22, 26, and 29 under the written description requirement of Section 112, first paragraph, because he considered the amendments made to independent Claim 1, upon which Claims 3 to 8, 16, 20 to 22, 26, and 29 are dependent, in the Reply dated October 5, 2005 to constitute the addition of new matter.

Applicants disagree with the Examiner's characterization of the amendment as adding new matter. Nevertheless, the Examiner's rejection has been overcome by the present amendment to independent Claim 1 which deletes the matter objected to. Claim 1 now defines the compound as comprising a polypeptide comprising an sFv molecule and an effector segment comprising a cysteinyl residue and a nucleic acid binding moiety coupled to the polypeptide by the residue. This is adequately supported in the application as stated above.

**Discussion of the Examiner's Rejection  
Under the Enablement Requirement of Section 112, First Paragraph**

The Examiner rejected Claims 1 to 8, 16, 20 to 22, and 29 under the enablement requirement of Section 112, first paragraph. The Examiner considers the compound of the present invention to be known to bind only erbB-2 antigen and has thus asserted that applicants have not enabled the use of such a compound in the delivery of a nucleic acid to any cell since not all cells express the erbB-2 antigen. The Examiner has asserted also that the application enables only the use of this compound to deliver a nucleic acid to cells *in vitro* and not *in vivo*.

The Examiner appears to base his rejection on his belief that sFv is a specific molecule which is capable of only binding erbB-2. This is not true. As stated in, for example, U.S. Patent No. 5,888,773, the Fv portion of an antibody is the smallest fragment to bear the complete antigen-binding site. It comprises the N-terminal variable (V) domains of the heavy (H) and light (L) chain. A single chain Fv (sFv) is a genetically engineered single-chain molecule that comprises these two domains connected by a linker and that has the antigen-binding function of the parental antibody. The present invention resides in the conjugation of such an sFv molecule with a nucleic acid binding moiety using an effector sequence comprising a cysteinyl molecule. sFv molecules may be based on antibodies which bind to antigens other than erbB-2. Indeed sFv molecules which bind to antigens other than erbB2 are described in the above patent. Further, methods for making sFv molecules are described in U.S. Patent No. 5,091,513. Accordingly, applicants submit that the use of sFv molecules other than those which bind to erbB-2 would be readily understood by those of skill in the art and, given such knowledge, it would not require undue experimentation to construct the compound of the present invention. In any event, the Examiner's ground for rejection should not apply to Claim 29 as amended as it now defines the compound as being one for use in targeting a cell which expresses erbB-2.

Regarding enabling the *in vivo* use of the compound, applicants refer the Examiner to Example 11 (page 46 to 49) of the application which describes the transfection of 3T3-HER2 cells using the gene delivery compounds of the present invention and comprising the following conjugates: C6ML3-9 sFv'-H1, C6ML3-9 sFv'-P1, and C6ML3-9 sFv'-SP. The transfection was conducted successful in the presence of serum which mimics *in vivo* conditions.

In the Action, the Examiner considered the above argument to be absurd since cell lines are invariably cultured in serum. This, however, does not negate the fact that transfection was conducted in the presence of serum and that the presence of serum mimics *in vivo* conditions more closely than, for example, an experiment conducted in pure buffer or saline. Applicants are not required to actually demonstrate the use of the invention *in vivo* to enable its use in *in vivo* environments. As known to those of skill in the art, serum is a bodily fluid and contains various molecules which are not present in artificial conditions. As such, it mimics *in vivo* conditions and applicants submit that the use of serum provides an adequate showing to enable the use of the invention *in vivo*.

The Examiner argues also that the tumor cells used in the above experiment express erbB-2 surface antigens only because they were first transfected with HER2 and, therefore, such cells might not mimic the surface conditions of a cell as it would appear *in vivo*. Applicants submit, respectfully, that this argument is incorrect. In the first instance, the Examiner has no basis to assert that the tumor cells were first transfected with HER2. Applicants used a cell line that already expressed erbB-2 and did not manufacture such a cell line. Secondly, as these cells were cultured *in vivo*, it is expected that the surface of such cells would indeed mimic the surface of cells *in vivo*.

### Conclusion

For the reasons expressed above, applicants request respectfully that the Examiner reconsider and withdraw his rejections. An early and favorable action is requested respectfully.

SYNNESTVEDT & LECHNER LLP  
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• Attorney Docket No. P 23,611-A USA

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Art Unit 1632

The Examiner is invited to telephone the undersigned to discuss matters that the Examiner believes may be relevant to placing the application in condition for allowance.

Respectfully submitted,



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